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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,321	07/13/2001	Yousuke Takahama	31671-173265	2334

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,321	TAKAHAMA, YOUSUKE	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response also filed on 8/3/05 has been entered. Claims 1-19 are pending in the instant application. This application contains claims 13-19 drawn to an invention non-elected without traverse in the response received on 11/03/03. Claims 13-19 are therefore withdrawn. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1-12 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Rejections - 35 USC § 112

The rejection of claims 9-12 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn over claims 10-12 in view of applicant's amendment to the claims, and maintained in modified form over claim 9.

The previous office action stated that claim 9 lacked antecedent basis for "the foreign gene" in line 4, as claim 9 recites a method of sustaining a gene therapeutic effect caused by a "foreign DNA". The applicant has amended claim 9 to recite " a foreign DNA", thus overcoming the lack of antecedent basis. However, as amended, the method steps refer to

transfecting immature T lymphocytes with "a foreign gene" and introducing the cells into a thymus where the foreign gene is expressed, whereas the preamble of the claim recites that the method is for avoiding immune response caused by "a foreign DNA", not a foreign "gene". As such, it is unclear how the method steps relate to the preamble of the method as claimed. It is suggested that the amendment amend either the preamble to recite "a foreign gene", or the body of the method claim to recite "a foreign DNA".

Claim Rejections - 35 USC § 103

The rejection of claims 1-12 under 35 U.S.C. 103(a) as being unpatentable over Ilan et al. (1996) J. Clin. Invest., Vol. 98 (11), 2640-2647, in view of DeMatteo et al. (1997) J. Virol., Vol. 71 (7), 5330-5335, and further in view of Bakker et al. (1999) J. Immunol., Vol. 162, 3456-3462, is maintained. Applicant's amendments to the claims and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant again presents arguments against each of the cited references individually and then states that even in combination the cited references do not teach the claimed invention. The applicant states that none of the cited references teach or suggest the basic technical feature of the invention, which is using immature T lymphocytes to acquire natural immunological tolerance. This is not agreed for reasons of record. As set forth in the rejection of record, the combination of the teachings of the cited references provides motivation and a reasonable expectation of success for using transfected immature T lymphocytes to induce tolerance to

foreign gene products expressed from the immature T lymphocytes. It is further noted that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Furthermore, the applicant is reminded that it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). In addition, it is noted that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In the instant case, Ilan et al., the primary reference, was cited for teaching the administration of cells transduced with the recombinant adenovirus into the thymus (Ilan et al., page 2640). Specifically, Ilan et al. teaches that in mammals pretreated by thymic injection of cells infected with recombinant adenovirus encoding a therapeutic gene such as human BUGT1, a second intrahepatic injection of the recombinant adenovirus resulted in sustained gene expression of at least 7 weeks (Ilan et al., page 2640). Ilan et al. further teaches that proteins other than BUGT1 can be used to generate central tolerance, such as proteins associated with autoimmune disease or allograft rejection (Ilan et al., page 2641, column 1). Thus, Ilan et al. was

cited for establishing that cells containing and expressing foreign DNA can be used to induce tolerance against the foreign gene by directly administering the cells to the thymus. The applicant argues that Ilan et al. does not render the instant invention obvious because Ilan et al. only teaches the administration of hepatocytes transfected with a foreign gene into the thymus and does not teach or suggest using transfected immature T lymphocytes. However, the rejection of record is not based solely on the teachings of Ilan et al. Both DeMatteo et al. and Bakker et al. were cited to supplement the teachings of Ilan et al. The applicant then states that neither DeMatteo et al. nor Bakker et al. teach the critical feature of the instant invention, i.e. the use of immature T lymphocytes to induce tolerance, and that as none of the three references specifically teaches this limitation, the invention as claimed is not rendered obvious by any combination of the cited references. In response, the applicant is again reminded that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The office recognizes that each reference individually does not render the instant invention obvious, however, the office has established that the combined teachings of Ilan et al., DeMatteo et al., and Bakker et al. render the instant invention obvious.

The applicant further argues that since Ilan et al. does not teach the use of immature T lymphocytes to induce tolerance in the thymus that Ilan et al. does not teach the mechanism for achieving tolerance envisioned by the applicants, i.e. that tolerance is achieved through differentiation of the immature T lymphocytes in the thymus. However, applicant's conclusion that because Ilan does not teach the advantage of the alleged mechanism for tolerance induction,

Ilan cannot be used alone or in combination to demonstrate the obviousness of the invention is incorrect. The MPEP states that the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991). MPEP 2144.

The motivation to modify the teachings of Ilan et al. with the teachings of DeMatteo et al. and Bakker et al., in other words the motivation to administer transduced immature T lymphocytes into the thymus to induce tolerance, is of record and is reiterated as follows. To supplement the teachings of Ilan et al., the rejection of record relies first of the teachings of DeMatteo et al. who teaches that adenovirus is capable of infecting immature T lymphocytes in neonatal thymus and further that the transduced neonatal T lymphocytes induce tolerance (DeMatteo et al., page 5330, abstract, and Figure 1). Note in particular that DeMatteo et al. teaches that it is the expression of the transgene in the neonatal T lymphocytes before maturation that induces tolerance. It was also noted in the rejection of record that DeMatteo et al. teaches that by using a cellular carrier to prevent viral extravasation into the periphery, adverse systemic reactions to adenovirus can be avoided (DeMatteo et al., page 5334, column 2). Thus, DeMatteo et al. supplements the teachings of Ilan et al. by teachings that immature T lymphocytes already present in the neonatal thymus can be transduced to express a foreign gene and that these transduced immature T lymphocytes induce tolerance. DeMatteo et al. also teaches, as does Ilan et al., that instead of directing administering the adenovirus encoding the foreign gene to the

lymphocytes in the thymus, cellular carriers can be used, i.e. transduced cells. Thus, DeMatteo et al. demonstrates that cell types other than hepatocytes are useful in inducing tolerance in the thymus, and in particular demonstrates that immature T lymphocytes transduced with adenovirus induce tolerance in the thymus.

Bakker et al. was then cited to further supplement Ilan et al. and DeMatteo et al. by teaching methods of infecting immature T lymphocytes with recombinant adenovirus *in vitro* in fetal thymic organ culture (Bakker et al., page 3457). Bakker et al. was also cited for teaching that fetal thymocytes infected with adenovirus develop into single positive mature T lymphocytes which ultimately migrate to the periphery (Bakker et al., page 3458, Figure 1, and page 3456).

As both Ilan et al. and DeMatteo et al. teach that mature T cells must be suppressed in the adult thymus in order to get tolerance induction and that cells transduced with adenovirus can be administered to the thymus to induce tolerance, and Bakker et al. teaches that immature thymocytes transduced with adenovirus develop into mature T lymphocytes and repopulate the periphery, the skilled artisan would have been motivated to administer adenovirus transduced immature T lymphocytes instead of transduced hepatocytes in the methods of Ilan et al., in order to both successfully generate tolerance to the adenovirus expressed proteins and to repopulate mature T lymphocytes in the periphery following the step of immunosuppression in the Ilan method. Therefore, in view of the need to suppress mature T cells in order to effectively achieve central tolerance by administering adenoviral infected cells to the thymus as taught by both Ilan et al. and DeMatteo et al., and further in view of the ability of transduced immature T lymphocytes to not only induce tolerance in the thymus but also to develop into mature T

lymphocytes capable of populating the periphery as taught by DeMatteo et al. and Bakker et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to induce tolerance by administering transduced immature T lymphocytes into the thymus instead of transduced hepatocytes in order to both induce tolerance to the heterologous gene products expressed in the transduced immature T lymphocytes and stimulate repopulation of the periphery with mature T lymphocytes. Further, based on the successful infection of immature fetal T lymphocytes in culture taught by Bakker et al., and the art recognized ability of immature lymphocytes in the thymus to induce tolerance as taught by DeMatteo et al., the skilled artisan would have had a reasonable expectation of success in infecting immature T lymphocytes with the recombinant therapeutic adenoviruses taught by Ilan et al. and using those infected immature T lymphocytes to induce central tolerance in adult hosts following intrathymic injection.

In regards to DeMatteo et al. and Bakker et al., the applicant argues that DeMatteo et al. does not teach "fetal thymus" and that Bakker et al. does not teach that the gene transferred T lymphocytes can be used for gene transfer. In response, DeMatteo et al. teach neonatal thymus, which is similar to fetal thymus in that the T lymphocytes contained in the neonatal thymus have yet to undergo maturation (see DeMatteo et al., abstract). Thus, the T lymphocytes in the neonatal thymus referred to in DeMatteo et al. are immature T lymphocytes. In response to applicant's arguments regarding Bakker et al., the rejection of record does not rely on Bakker et al. for teaching or suggesting the transplantation of the transduced immature fetal T lymphocytes, both Ilan et al. and DeMatteo et al., as discussed in detail above, already provide the requisite teachings and suggestion for using transduced cells to deliver foreign genes to the thymus for tolerance induction. Bakker et al. was cited for providing a reasonable expectation of

success for transducing immature T lymphocytes in cell culture rather than *in vivo* as taught by DeMatteo et al. and further for providing teachings that immature fetal thymocytes infected with adenovirus develop into single positive mature T lymphocytes which can repopulate the periphery. Thus for reasons of record as discussed in detail above, applicant's arguments have not been found persuasive and the rejection of record stands.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your

application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER